



These sections of small intestine from normal mice (left panel) and mutant, *Cdx2*-deficient mice (right panel) show overall disorganization in the mutant mouse intestine, as well as aberrant production of proteins typically found in the upper gastrointestinal tract (esophagus). Smaller inset boxes show magnified images. As described in this chapter, researchers have identified *Cdx2* as an essential factor controlling formation of normal small intestine, with implications for some intestinal conditions that affect humans as well.

Images provided by Dr. Klaus H. Kaestner and reprinted from Developmental Cell, 16, Gao N, White P, and Kaestner KH, Establishment of intestinal identity and epithelial-mesenchymal signaling by Cdx2, 588-599, Copyright 2009, with permission from Elsevier.

Digestive Diseases and Nutrition

Digestive diseases are among the leading causes of doctor visits, hospitalization, and disability in the U.S. each year. These conditions span a wide spectrum of disorders that affect the gastrointestinal (GI) tract, liver, gallbladder, and pancreas, as well as obesity and other nutrition-related disorders. In 2004, over 35 percent of all emergency and outpatient hospital visits—some 100 million—were associated with a diagnosis of a digestive disease.¹ With some being very common and others quite rare, digestive diseases, collectively, exact a significant toll on public health in terms of their effects on quality of life, years lost due to death, and costs associated with hospitalization and pharmaceutical and surgical interventions. To reduce the public health burden associated with digestive diseases, NIDDK-supported scientists are vigorously pursuing research to understand how widespread these diseases are across the U.S., to identify the causes of these diseases and how they progress, and to test new interventions for prevention and treatment of these costly diseases, including drugs, surgery, and behavior modification.

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are marked by destructive inflammation in the intestinal tract leading to rectal bleeding, diarrhea, nutritional deficiencies, and other serious complications. IBD often strikes early in life, with a peak age of onset in adolescence or young adulthood. To address this condition, surgery may be required, including removal of the affected region of the intestine. Scientists are dissecting the complex interactions among the genetic, environmental, and cellular factors that contribute to the development of IBD. The continued discovery of predisposing genetic variations and potential autoimmune and microbial influences will help catalyze the design of novel therapeutic strategies.

Research on controlling intestinal inflammation has potential benefits not only for patients with IBD, but also for those at risk of developing colorectal cancer. Screening programs for colorectal cancer are aimed at reducing mortality through early detection, particularly in those individuals at higher risk.

Intestinal disorders also include functional bowel disorders, which result in symptoms of abdominal pain and altered bowel habits. For example, irritable bowel syndrome (IBS) causes pain and constipation or diarrhea. IBS more frequently affects women, who may display a different range of symptoms and respond differently from men to pharmacologic treatments

for the disease. While diet and stress contribute to this disorder, its underlying causes are unknown. Gastroesophageal reflux disease, in which stomach acids rise up into the esophagus, is a common functional bowel disorder that can lead to a condition known as Barrett's esophagus. This condition, in which cells lining the esophagus transform into an intestinal-type cell, is associated with a heightened risk of esophageal cancer, the most rapidly rising cancer in the U.S. Gastroparesis is another functional bowel disorder that is characterized by delayed emptying of food from the stomach, resulting in nausea, vomiting, and abdominal discomfort. A common cause of gastroparesis is diabetes, which is thought to damage nerves leading to the stomach and controlling movement of food. Fecal incontinence, or impaired bowel control, is another bowel disorder that poses a major public health burden, particularly in the elderly.

Some digestive diseases can be triggered by the body's reaction to certain foods. For example, in individuals with celiac disease, the immune system reacts to the protein gluten—a component of wheat,

¹ Everhart JE, editor. *The burden of digestive diseases in the U.S.* U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: U.S. Government Printing Office, 2008; NIH Publication No. 09-6443.

barley, and rye—and results in damage to the small intestine. This damage interferes with the ability of the intestine to absorb nutrients from foods and can result in chronic diarrhea, bloating, anemia, and, in children, growth failure. The only current treatment for celiac disease is maintenance of a strict gluten-free diet, which is difficult for many people. The greater challenge now facing patients and their health care providers is to improve methods capable of diagnosing celiac disease early, before damage occurs or other conditions develop. Recent and continued advances in the understanding of genes that predispose individuals to develop celiac disease may contribute to improved diagnosis in the future through genetic-based screening.

The microorganisms that inhabit the GI tract are important factors in maintaining or tipping the balance between digestive health and disease. The microbes can affect intestinal health in some surprising ways, depending on their interactions with each other, with host cells, and with nutrients ingested by their host. Scientists are gaining insights into the ways these GI microorganisms influence the development and function of the digestive tract, as well as other systems throughout the body such as those with immune and metabolic functions.

The liver is an organ within the digestive system that performs many centralized functions in the body, including metabolism and distribution of nutrients such as fats. When the liver is functionally compromised by disease, this can have serious adverse impacts on health and can sometimes lead to complete liver failure. Some liver diseases primarily affect children—such as biliary atresia, a progressive inflammatory liver disease—while others more commonly affect adults—such as a form of nonalcoholic fatty liver disease known as nonalcoholic steatohepatitis. Some are caused by viral infection such as hepatitis B and C, or by genetic mutations such as alpha-1-antitrypsin deficiency, while others arise from diverse factors such as autoimmune reactions, drug toxicity, and other triggers, some of which are unknown. Many of these forms of liver disease, such as chronic hepatitis C, place individuals at elevated risk for developing liver cancer. A healthy liver is necessary for life, and the only treatment for end-stage liver disease is a liver transplant. Because the number of livers available from deceased donors is limited, research is of critical importance to identify liver disease, preserve

liver function in people with liver disease, and develop new treatment options, including transplants performed with liver tissue from living donors.

The number of Americans who are overweight or obese has risen dramatically in recent decades and is now at epidemic levels. Obesity is associated with numerous serious diseases, including type 2 diabetes, heart disease, and cancer. Multiple factors contribute to obesity. As scientists elucidate the molecular, genetic, and environmental factors that influence appetite, metabolism, and energy storage, they are identifying potential avenues for the development of new intervention strategies to promote safe, long-term weight loss. In addition to new pharmacologic interventions for obesity, existing bariatric surgical techniques are being evaluated for their long-term impacts on weight loss and well-being. Investigators are also continuing research to help people achieve healthy lifestyles that include physical activity and improved diet. (Additional information on NIDDK-supported research endeavors focusing on obesity is provided in the Obesity chapter.)

GENETICS OF INFLAMMATORY BOWEL DISEASES

New Genetic Risk Factors Identified for

Ulcerative Colitis: An international research group, including investigators from the NIDDK's IBD Genetics Consortium, has identified new genetic risk factors associated with ulcerative colitis (UC) through a genome-wide association study of over 1,000 people with UC compared to other individuals without the disease.

UC causes inflammation in the tissue lining the colon and rectum, which may result from abnormal immune responses within the intestines. Although UC shares some features with the other major form of IBD—Crohn's disease—other characteristics are distinct. Genome-wide association studies in recent years have identified genetic factors that contribute to each of these forms of IBD. These studies have been particularly fruitful in terms of uncovering genetic regions associated with Crohn's disease. In the current study, researchers intensified their efforts to identify additional genetic factors that increase susceptibility to UC.

To expand knowledge of genetic contributors to UC, researchers performed a genome-wide association study using DNA collected from individuals with or without UC who shared a similar ancestry, in order to minimize other genetic differences. With this method, they were able to identify chromosomal regions, as well as genes within some of those regions, that are associated with an increased risk of developing UC. Two chromosomal regions were linked for the first time to UC risk. Several genes located within or near these regions play a role in immune function and inflammation, and may contribute to disease susceptibility by altering these processes. Additional genetic factors previously implicated in UC and Crohn's disease, including the immune system gene *IL-23R*, were also confirmed in this analysis. However, many genetic factors that had proven important for Crohn's disease risk were not associated with susceptibility to UC, suggesting that the two forms of IBD have overlapping but unique genetic profiles.

The identification of genetic regions associated with increased susceptibility to UC has the potential to inform understanding of disease processes unique to this form of IBD. Additionally, this knowledge can provide targets for developing new, more personalized therapeutic and preemptive approaches to controlling this disease.

*Silverberg MS, Cho JH, Rioux JD, McGovern DPB, Wu J, Annese V, Achkar JP, Goyette P, Scott R, Xu W, Barmada MM, Klei L, Daly MJ, Abraham C, Bayless TM, Bossa F, Griffiths AM, Ippoliti AF, Lahaie RG, Latiano A, Paré P, Proctor DD, Regueiro MD, Steinhart AH, Targan SR, Schumm LP, Kistner EO, Lee AT, Gregersen PK, Rotter JI, Brant SR, Taylor KD, Roeder K, and Duerr RH: Ulcerative colitis–risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 41: 216-220, 2009.*

SCREENING FOR COLON CANCER

Studies of Polyp Size Inform New

Recommendations: Scientists have provided recommendations for managing patients with colon polyps based on new evidence of the relationship of polyp size to the risk of colon cancer. These recommendations have been incorporated into new screening guidelines to better predict and prevent colon cancer.

Imaging methods being used for colon cancer screening—such as computer tomographic colonography (CTC)—are preferred by some patients and clinicians to colonoscopy, but they present new challenges. Although these methods can detect polyps and assess their size, unlike colonoscopy, they do not provide a way to detect tissue abnormalities or remove cancerous or pre-cancerous polyps (polypectomy). Clinicians must decide which patients with polyps detected by these methods should receive follow-up colonoscopy and polypectomy. Information on how polyp size relates to colon cancer risk would help to inform the best screening and management practices.

To gain insight into how polyp size indicates whether a polyp is likely to become cancerous, scientists analyzed reports on screening colonoscopies of asymptomatic patients. Polyps that were identified during the colonoscopies were removed and analyzed for tissue abnormalities. Patients with polyps were grouped by the size of their largest polyp, and the polyps were categorized according to their tissue characteristics. Analyses of polyp size and abnormalities supported current screening guidelines that patients with large polyps should be offered colonoscopy and polypectomy based on the high risk that the polyp was pre-cancerous. The study results also agreed with current guidelines stating that small polyps present very low risk; therefore, most of these patients could be followed safely with periodic imaging rather than polyp removal, although additional research was recommended. Notably, the study analyses indicated that intermediate-size polyps present a substantial risk. Based on these results, it was recommended that patients with mid-size polyps should be offered colonoscopies and polypectomies. Also, the scientists suggested that another study be conducted to assess the cost-effectiveness of image-based screening for colon cancer if a significant number of patients will require follow-up colonoscopies under these new recommendations.

Current colon cancer screening and management guidelines, written by several professional societies, have been updated to reflect the recommendations of this study regarding use of colonoscopy and polypectomy depending on polyp size. For patients with polyps, this more informed management strategy should improve their care and chances of avoiding colon cancer.

Lieberman D, Moravec M, Holub J, Michaels L, and Eisen G: Polyp size and advanced histology in patients undergoing colonoscopy screening: Implications for CT colonography. *Gastroenterology* 135: 1100-1105, 2008.

INTESTINAL DEVELOPMENT, HOST DEFENSE, AND WOUND REPAIR

Master Regulator of Intestinal Development

Identified: Scientists have found that a single gene plays an essential role in controlling normal intestinal development. *In utero*, the GI tract develops from the foregut, which becomes the esophagus, stomach, and upper part of the small intestine; the midgut, which gives rise to the small intestine; and the hindgut, which forms the cecum and colon. The formation of the intestine is directed by a complex network of precisely timed signals passing between and within cells of these developing tissues, including layers of cells that will form the lining of the intestine (epithelial cells) and cells that will form intestinal smooth muscle and other intestinal tissues (mesenchymal cells). Some of these signals are so essential for life that, when mutated, the resulting deficiency causes death *in utero*. For example, mutation of a mouse gene important to intestinal development, called *Cdx2*, is lethal for mice at the embryonic stage. Humans also carry a form of this gene, referred to as *CDX2*.

To investigate the role that the *Cdx2* gene plays specifically in development of the intestine, scientists created a mouse model in which the *Cdx2* gene is only mutated in developing intestinal cells; with this restricted *Cdx2* deficiency, the developing mice do not die *in utero* and can thus be studied. When the scientists compared this mutant mouse model with normal mice, they observed some dramatic and surprising changes in the development of the intestine. For example, the colon in the mutant mouse failed to develop correctly, mimicking a disorder in humans known as colonic atresia. Also, epithelial cells on the inner layer of the intestine did not differentiate to form the correct cell types and structures, such as villi with brush border membranes needed for nutrient absorption. Instead, the mutant epithelial cells more closely resembled cell types found in the upper GI tract, specifically the esophagus, rather than those found in a normal intestine. Analyses of the “transcriptome”—the collection of

genes turned on (expressed)—in the small intestine confirmed that the *Cdx2*-deficient small intestine had converted to a more esophageal type by turning on genes typically seen in the esophagus but not the intestine. As the intestine develops, *Cdx2* production normally becomes restricted to epithelial cells. However, the researchers showed that cells of the other tissue layers within the intestine were also altered to be more esophagus-like, suggesting that *Cdx2* deficiency-related epithelial modifications subsequently caused changes in adjacent tissue layers, converting them to an esophageal program as well.

These experiments demonstrate the importance of *Cdx2* to proper intestinal development by characterizing the repercussions of its removal, including abnormal colon formation and a switch to an upper GI tract phenotype. Based on these findings, *Cdx2* is now recognized as playing a critical role in programming tissues along the length of the GI tract to have specific cell types and features to suit their different functional needs. Beyond informing our understanding of intestinal development, these studies have implications for human conditions in which intestinal programming is altered, such as colonic atresia.

Gao N, White P, and Kaestner KH: Establishment of intestinal identity and epithelial-mesenchymal signaling by *Cdx2*. *Dev Cell* 16: 588-599, 2009.

Specialized Cells in the Intestine Prevent Bacteria from Invading Other Tissues:

Scientists have recently conducted studies in mice that provide new insights into how specific cells lining the intestine detect and respond to resident bacteria and maintain a mutually beneficial relationship with the intestinal microbial community. The intestines of humans and other animals provide a home to billions of bacteria. This microbial community and our own cells have developed a symbiotic relationship in which bacteria provide essential metabolic functions in exchange for a nutrient-rich environment. It is important, however, that microbes in the gut do not spread to other tissues, where they could cause damage, and even death. Resident bacteria are confined to the gut by a layer of cells that make up the intestinal lining. A specialized type of these cells, known as Paneth cells, protects the host against breaches in the intestinal barrier by

initiating an antimicrobial response, which could target either normal gut bacteria or invading pathogens. Given the protective importance of this response, scientists are interested in understanding how Paneth cells detect bacteria to initiate the antimicrobial program that helps maintain symbiotic balance in the gut.

To understand the role of Paneth cells in detecting and responding to intestinal bacteria, scientists carried out experiments in mice lacking a key cellular signaling protein, called MyD88. In these experiments, they found that mice lacking MyD88 in all of their cells were unable to initiate an antimicrobial response. However, reintroduction of MyD88 specifically into Paneth cells—but not other types of cells—of these mice was sufficient to stimulate the antimicrobial response to gut bacteria. This result demonstrated that Paneth cells directly detect bacteria to stimulate MyD88 activation, rather than relying on signals from MyD88 activation in neighboring cells. The scientists went on to show that mice lacking MyD88 also had increased numbers of bacteria in tissues outside of the intestine compared to normal mice. By looking further at mice that do not have Paneth cells, they showed that MyD88 signaling in Paneth cells is essential for restricting the movement of gut bacteria across the intestinal lining into host tissues.

This study showed that Paneth cells limit the penetration of bacteria across the intestinal barrier, perhaps by regulating how the bacteria interact with cells of the intestinal lining. Since elevated levels of bacteria associated with the intestinal lining have been observed in patients with IBD, these results may have important implications for understanding the pathology of the disease.

Vaishnava S, Behrendt CL, Ismail AS, Eckmann L, and Hooper LV: Paneth cells directly sense gut commensals and maintain homeostasis at the intestinal host-microbial interface. Proc Natl Acad Sci USA 105: 20858-20863, 2008.

Immune Cell Protein Regulates Wound Repair in the Colon: By studying how injuries to the colon lining are repaired in normal and genetically-engineered mice, scientists have unveiled the role of an immune cell protein, called Trem2, in mediating efficient wound repair in the colon. Following injury to a tissue, the

body orchestrates an inflammatory response to stave off potential infections and repair the damaged tissue. This process is particularly important in the small and large intestines (including the colon), where a lining of cells, called epithelial cells, provides the barrier between the inside (lumen) of the intestines and the deeper tissue layers, as well as surrounding tissues. Since the lumen of the intestines is home to trillions of bacteria, some of which play essential roles in intestinal processes such as normal metabolism while others are potential pathogens, the integrity of the intestinal lining must be maintained to prevent the spread of harmful microbes within the gut and to other parts of the body. Therefore, any breaches in the intestinal barrier due to injury must be efficiently repaired to prevent localized and systemic infection.

To study the cellular and molecular basis for intestinal wound repair, scientists adapted a biopsy technique widely used on skin to generate uniform wounds in the colon of normal and genetically-engineered mice. By analyzing the regeneration process following biopsy injury, the scientists found that wound healing occurred in two phases. In the first phase (1-2 days after injury), a single layer of cells formed over the wound area by contraction of the surrounding tissue where stem cells were located. Subsequently, there was an increase in epithelial cell growth and division adjacent to the wound area and an increase in the number of immune cells in the wound bed during the second phase (2-4 days after injury). More importantly, the scientists found that the two phases of wound healing were associated with the presence of different types of immune cells and the chemicals they release, known as cytokines, in and around the wound bed. In addition, they showed that the switch from phase 1 to phase 2 of wound healing is triggered by a protein known as Trem2, which is located on the surface of immune cells called macrophages. Genetically-engineered mice that lacked Trem2 on their macrophages exhibited a sustained increase in phase 1 signals and a reduction in phase 2 signals that resulted in slow and incomplete wound healing. Thus, cellular signaling through Trem2 is important for promoting efficient healing of colonic wounds.

With a better understanding of the cellular and molecular components of wound healing in the colon, the researchers plan further studies to support their

model in which Trem2 subdues pro-inflammatory signals associated with phase 1, and boosts phase 2 signals to promote efficient wound healing. Understanding the molecular components of this process may provide targets for patients with defects in barrier function or immune cell activation that result in impaired colon repair following injury.

Seno H, Miyoshi H, Brown SL, Geske MJ, Colonna M, and Stappenbeck TS: Efficient colonic mucosal wound repair requires Trem2 signaling. Proc Natl Acad Sci USA 106: 256-261, 2009.

NEW THERAPEUTIC STRATEGY TO TREAT BARRETT'S ESOPHAGUS

Treating Pre-Cancerous Barrett's Esophagus:

Barrett's esophagus has been treated successfully in a clinical trial using a nonsurgical procedure known as radiofrequency ablation (RFA). Barrett's esophagus is a condition that can result from gastroesophageal reflux disease. This happens when stomach acids flow back up into the esophagus, causing the cells lining the esophagus to transform into a type of cell that normally lines the intestine. In some patients with Barrett's esophagus, these cells continue to change, first becoming pre-cancerous and then developing into a deadly form of cancer known as esophageal adenocarcinoma. Currently, the only treatment for esophageal cancer is surgical removal of the esophagus. It has not been clear how best to treat Barrett's esophagus in which there are abnormal, pre-cancerous cells.

In a multi-center clinical trial supported by the NIDDK, patients with pre-cancerous Barrett's esophagus were divided into two groups and treated with either RFA or a "sham" procedure. RFA is an outpatient procedure using a catheter with a small balloon attached to its end that is inserted into the esophagus. When it is in place, the inflated balloon radiates heat, discretely destroying only the adjacent layers of abnormal cells lining the esophagus of the patient with pre-cancerous Barrett's esophagus. RFA is also less invasive than surgery, although this study did not assess the relative efficacy of surgery. The "sham" procedure given to the control group consisted of insertion of the catheter without destruction of abnormal tissue. Patients were given up to four RFA or "sham" sessions and then evaluated at the end of the year-long study period. When the

RFA-treated patients were evaluated, most no longer had pre-cancerous esophageal cells. Only a very small number of RFA-treated patients had progression of their disease, and although some patients had reverted to early stage (not pre-cancerous) Barrett's esophagus, the majority of RFA-treated patients now had normal esophageal tissue. In contrast, only a small number of patients receiving the "sham" treatment improved, and a much larger number than the RFA group had disease progression. This study presents important findings by demonstrating that the RFA outpatient procedure is highly effective in treating Barrett's esophagus and reducing the risk that this disease will develop into a deadly form of esophageal cancer.

Shaheen NJ, Sharma P, Overholt BF, Wolfsen HC, Sampliner RE, Wang KK, Galanko JA, Bronner MP, Goldblum JR, Bennett AE, Jobe BA, Eisen GM, Fennerty MB, Hunter JG, Fleischer DE, Sharma VK, Hawes RH, Hoffman BJ, Rothstein RI, Gordon SR, Mashimo H, Chang KJ, Muthusamy VR, Edmundowicz SA, Spechler SJ, Siddiqui AA, Souza RF, Infantolino A, Falk GW, Kimmey MB, Madanick RD, Chak A, and Lightdale CJ: Radiofrequency ablation in Barrett's esophagus with dysplasia. N Engl J Med 360: 2277-2288, 2009.

CELIAC DISEASE RESEARCH

The Growing Burden of Undiagnosed Celiac

Disease: Scientists have found evidence that the number of people with undiagnosed celiac disease has grown over the past 50 years, placing more individuals at a greater risk of premature death. Celiac disease is an autoimmune disease caused by intolerance of the gluten proteins found in many grains, which can be treated very effectively with a gluten-free diet. However, this disease often goes undiagnosed and untreated, often causing severe health problems.

To determine the consequences of undiagnosed celiac disease and to clarify whether its prevalence has changed over the past several decades, scientists used blood samples from three different groups of individuals to test for two antibodies associated with celiac disease. Samples from a group of U.S. Air Force personnel had been taken and stored frozen 45 years earlier, and were shown to be well-preserved. More recent samples were obtained from an older group of men with birth dates similar to those of the Air Force

personnel and from a younger group who were similar in age to the Air Force personnel when they were sampled. Individuals with both of the celiac-specific antibodies were considered to have undiagnosed celiac disease. When scientists compared the death rates for Air Force personnel who had undiagnosed celiac disease with those who did not, they discovered that death rates from all causes were nearly four-fold higher for those with undiagnosed celiac disease. Analyses comparing samples from the Air Force group with those from the older and younger groups tested revealed that the prevalence of undiagnosed celiac disease has increased more than four-fold over the past 50 years.

This study presents a dramatic picture of the rapidly increasing rate of undiagnosed celiac disease and its impact on the U.S. population. Its findings illustrate the importance of alerting clinicians and the public to this multi-symptom, often-overlooked disease so that diagnosis can be made before severe health problems develop. Toward this end, the NIDDK's Celiac Disease Awareness Campaign informs health care personnel and the public about celiac disease, its treatment, and its consequences. The Campaign can be accessed at www.celiac.nih.gov/

Rubio-Tapia A, Kyle RA, Kaplan EL, Johnson DR, Page W, Erdtmann F, Brantner TL, Kim WR, Phelps TK, Lahr BD, Zinsmeister AR, Melton LJ 3rd, and Murray JA: Increased prevalence and mortality in undiagnosed celiac disease. Gastroenterology 137: 88-93, 2009.

Molecular Basis for Immune Reactivity to Dietary Gluten in Celiac Disease:

Researchers supported by NIDDK have uncovered how a variant of an immune system molecule associated with celiac disease contributes to increased immune reactivity towards dietary gluten. Celiac disease is an autoimmune disease in which an aberrant immune response to the gluten protein found in dietary grains, such as wheat, barley, and rye, results in chronic inflammation and tissue damage in the intestine. The increased gluten sensitivity in a subset of celiac patients is strongly associated with HLA-DQ8, a variant of the HLA protein molecule that is found on the surface of cells. Normally, HLA molecules present potentially harmful substances to the immune system. In patients with celiac disease, however, HLA-DQ8 presents fragments

of gluten proteins to immune system cells, called T cells, via “receptors” on these cells, known as T-cell receptors (TCRs). This interaction initiates an aberrant immune response against the gluten protein. However, it is not fully understood how this particular version of the HLA molecule interacts with gluten and generates an immune response.

Previous studies have shown that the HLA-DQ8 protein has a sequence variation compared to other HLA molecules, which confers a preference for detecting protein fragments classified chemically as having a negative charge. Although gluten fragments do not inherently contain negative charges, they can be modified by cellular enzymes to contain negative charges. This modified gluten fragment is thought to elicit the HLA-DQ8-mediated immune response. In the present study, scientists showed that while the modified, negatively charged gluten fragment has a functional advantage in eliciting an immune response, HLA-DQ8 can detect and generate an immune response to the unmodified, native fragment as well. They found that the ability to incite an immune response to both modified and unmodified gluten fragments requires signaling through different sets of TCRs. For the negatively charged fragment, an immune response is generated by signaling through a broad repertoire of TCRs that possibly recognize the fragment in slightly different ways. In contrast, a very limited set of TCRs is used to detect the unmodified, native gluten fragment. Analysis of TCR sequences showed that this limited set of TCRs contains a unique negative charge that is required for recognizing the unmodified, native gluten fragment. By introducing mutations that remove this negative charge from the TCR, the researchers found that the immune response to unmodified gluten fragments can be abolished. In addition, they found that sensitivity to the native, unmodified gluten fragment is associated with TCRs that all contain the conserved negative charge in cell lines derived from patients with celiac disease.

The results of this study reveal a new mechanism by which the immune cell molecule HLA-DQ8 detects gluten fragments to elicit an immune response in celiac disease. The researchers propose that the initial response to the native fragment followed by a much broader response to the modified fragment contribute to the amplified gluten sensitivity in celiac disease,

paving the way for further investigations into how this response contributes to disease onset and progression. Future research along these lines could also determine whether HLA-DQ8 contributes through a similar mechanism to type 1 diabetes, with which it has also been associated.

Hovhannisyan Z, Weiss A, Martin A, Wiesner M, Tollefsen S, Yoshida K, Ciszewski C, Curran SA, Murray JA, David CS, Sollid LM, Koning F, Teyton L, and Jabri B: The role of HLA-DQ8 beta57 polymorphism in the anti-gluten T-cell response in coeliac disease. Nature 456: 534-538, 2008.

RESEARCH ON HEPATITIS C

Long-Term Treatment with Common Hepatitis C Therapy Does Not Prevent Liver Disease

Progression: Results of a large, multi-center clinical trial provide strong evidence that long-term therapy with a standard antiviral drug used to treat chronic hepatitis C is ineffective at preventing disease progression in patients who did not initially respond to a shorter course of antiviral treatment.

Chronic hepatitis C is the major cause of cirrhosis and liver cancer in the U.S. The standard treatment for chronic hepatitis C—a combination of the antiviral drugs peginterferon and ribavirin given for 24 to 48 weeks—is associated with some side effects and is not effective for half of patients, for whom additional treatment options are currently limited. In those for whom standard treatment is ineffective, researchers investigated whether longer-term treatment with peginterferon might prompt a response in terms of reduced progression to cirrhosis and a form of liver cancer known as hepatocellular carcinoma.

The Hepatitis C Antiviral Long-term Treatment against Cirrhosis (HALT-C) trial was designed to test whether long-term antiviral therapy can prevent liver disease progression in people with advanced hepatitis C who did not respond previously to standard, short-term therapy. These individuals were given either peginterferon or no treatment for 3.5 years. Liver biopsies were collected to assess progression of disease to endpoints such as cirrhosis and hepatocellular carcinoma. Although levels of

key liver enzymes and levels of hepatitis C virus were significantly reduced in patients receiving peginterferon compared to those receiving no treatment, the treatment did not reduce progression of liver disease. This result indicates that there is no benefit to continuing peginterferon therapy long-term in those with chronic hepatitis C who do not respond to a standard course of antiviral therapy.

The results of this trial can help spare patients from ineffective long-term treatment and its side effects. The trial also provides renewed incentive to find new therapies for chronic hepatitis C, which may include some experimental agents currently in early stages of development.

Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, Lok AS, Bonkovsky HL, Morgan TR, Ghany MG, Morishima C, Snow KK, Dienstag JL, for the HALT-C Trial Investigators: Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 359: 2429-2441, 2008.

Scientists Discover Genetic Factors in Liver Cells Needed for Hepatitis C Virus Infection:

A team of scientists working in the NIDDK's intramural Liver Diseases Branch has applied genomic technology to identify genetic factors in liver cells that are used by the hepatitis C virus (HCV) for successful infection. Hepatitis C is one of the major causes of chronic liver disease in the U.S., and is a common cause of liver cancer. HCV invades liver cells of infected individuals, co-opting the cellular machinery to produce more copies of the virus. A wide spectrum of response to HCV infection is seen across individuals, in that some develop severe chronic liver disease while others spontaneously purge the virus. Available therapy for hepatitis C is effective in only some patients and can cause significant side effects. Some patients with hepatitis C are co-infected with the human immunodeficiency virus (HIV), further complicating their care.

Building on these observations and recent technological achievements, such as the development of a cell culture system for studying HCV, and genome-wide screening and RNA interference technology, these researchers

screened HCV-infected liver cells to identify genetic factors that are required for successful HCV infection. Using molecules called “small interfering RNAs” to selectively inhibit production of particular genetic factors within HCV-infected human liver cells, the scientists screened the effect of silencing different genes throughout the genome on viral production. The screen identified 30 genetic factors in the liver cells as being important for viral production—factors that were previously implicated in HCV infection—demonstrating the screen’s validity to correctly pick out meaningful factors. It also identified several previously unappreciated genetic factors in liver cells on which HCV depends for infection. The researchers compared their findings of genetic factors in liver cells needed for HCV infection to viral factors identified by an HCV infection mapping project to visualize important interactions between host and viral proteins. Comparison to other viruses related to HCV, such as the West Nile Virus, also revealed several host factors and mapped host-viral interactions used by both viruses to cause infection. This study also compared genetic factors in liver cells found to be important for HCV infection with those for HIV infection, revealing 10 liver cell factors in common that are used by both viruses.

This study provides a wealth of information on genetic factors in liver cells that enable HCV infection. Pursuit of these genetic leads has the potential to identify targets for future therapies that are personalized to be more effective in individuals whose HCV infection is unresponsive to current treatment. This work may also benefit those who are co-infected with both HCV and HIV by forming the basis for therapies that target host genetic factors on which both viruses depend.

Li Q, Brass AL, Ng A, Hu Z, Xavier RJ, Liang TJ, and Elledge SJ: A genome-wide genetic screen for host factors required for hepatitis C virus propagation. Proc Natl Acad Sci USA. 106: 16410-16415, 2009.

GENETICS OF PRIMARY BILIARY CIRRHOSIS

Genetic Variants Linked to Autoimmune Disease Targeting Bile Ducts: Researchers have identified several genetic variants that are commonly found in

patients with primary biliary cirrhosis. In this chronic autoimmune disease, the bile ducts in the liver become inflamed and damaged and, ultimately, disappear. When this happens, bile—a liquid produced in the liver and released through bile ducts to aid digestion of dietary fats in the intestine—builds up in the liver and leads to liver damage, cirrhosis, and end-stage liver disease. The initial inflammation and damage to bile ducts is believed to result from an autoimmune response in which the body’s immune system inadvertently attacks and destroys specific cells lining the bile ducts. While scientists know the molecular factor that elicits the immune response, it is not fully understood why this molecule is inappropriately targeted in the first place. Like other autoimmune diseases, scientists think that the underlying cause of primary biliary cirrhosis has a strong genetic component. However, no genetic factors had been conclusively identified that point to a cause for primary biliary cirrhosis.

To facilitate the identification of possible genetic links to primary biliary cirrhosis, NIDDK-supported scientists recently carried out a genome-wide association analysis of DNA samples from patients with the disease compared to healthy controls. In this type of study, scientists scan the genomes of thousands of individuals and look for genetic variants that are more likely to be associated with a particular trait or condition such as, in this case, primary biliary cirrhosis. By scanning the genomes of over 500 patients with primary biliary cirrhosis and over 1,500 healthy individuals, this analysis identified several genetic variants in three specific regions—or loci—of the genome that are more frequently found in the patient group (and not the healthy control group). One of these regions, called the *HLA* locus, codes for proteins that are important for presenting molecules to the immune system to initiate the immune response; variants in genes coding for particular HLA proteins are often associated with other autoimmune diseases. The other two regions lie within the *IL12A* and *IL12RB2* genetic loci, which code for a pair of proteins—interleukin-12 (IL-12) and the IL-12 receptor—that are critical for cellular communications to propagate the inflammatory immune response. By conclusively associating genetic variants in these loci with primary biliary cirrhosis, this study sheds light on the “immunogenetic” basis of this disease and

points to the IL-12 signaling pathway as a potential therapeutic target for treating patients.

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CN, Coltescu C, Atkinson EJ, Heathcote EJ, Lazaridis KN, Amos CI, and Siminovitch KA: Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. N Engl J Med 360: 2544-2555, 2009.

Childhood Liver Disease Research and Education Network

Although liver diseases are considered rare during childhood, those that do occur tend to be severe and progressive, often occur for unknown reasons, and have limited effective medical therapies. In June 2009, in an effort to improve the understanding of pediatric liver disease and to improve the care of children with these conditions, NIDDK established the Childhood Liver Disease Research and Education Network (ChiLDREN). ChiLDREN, which is a collaborative team of doctors, scientists, medical facilities, and patient support organizations, brings together ongoing clinical research efforts of the Biliary Atresia Research Consortium (BARC) and the Cholestatic Liver Disease Consortium (CLiC) under one cohesive network. The consolidation of BARC and CLiC resources into one network will better enable clinicians to conduct clinical trials, facilitate the discovery of underlying causes of disease, and lead to the development of new diagnostic and treatment options for children with liver disease.

BARC was initially funded by NIDDK in 2002 to further understand the causes of and develop treatments for biliary atresia, the most common, severe liver disease in children. In children with this condition, the abnormal formation or absence of bile ducts results in the blockage of bile flow from the liver (cholestasis) and liver injury. Although surgical procedures are available to treat children with biliary atresia, these procedures are usually not curative and most children will eventually require a liver transplant; biliary atresia is the most common cause for liver transplants in children. The causes of this disease are unknown.

To better understand the causes of biliary atresia and develop improved treatments, BARC is currently carrying out several clinical studies. In two of these studies, clinicians are collecting clinical information and biological samples (tissues and body fluids) from infants and children with biliary atresia. These types of prospective, observational studies will allow researchers to identify potential causative factors that lead to disease onset and follow the natural history of disease progression. In a third clinical trial, researchers are evaluating the use

of corticosteroid therapy following the standard surgical procedure—known as the Kasai procedure—for treating infants with biliary atresia, with the hope of improving the long-term benefits of surgery and reducing the need for liver transplant in infants with biliary atresia.

While biliary atresia does not appear to be an inherited condition, several other cholestatic liver diseases have an inherited genetic basis. Initially established in 2004 as part of the NIH Rare Disease Clinical Research Network and now part of the NIDDK-funded ChiLDREN, CLiC is studying five distinct genetic causes of inherited pediatric cholestatic liver disease: Alagille syndrome, alpha-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, bile acid synthesis defects, and mitochondrial hepatopathies. The major goal of CLiC is to follow the natural history and progression of these diseases. In an ongoing clinical study, called Evaluating the Genetic Causes of Progression of Cholestatic Liver Diseases, researchers are collecting clinical information, family history, and biological samples from children with cholestatic liver diseases, so as to develop a better understanding of the causes and effects of these diseases. Progress in identifying the molecular and biochemical causes will offer researchers new opportunities for developing therapeutic interventions.

In a new area of research, CLiC has recently expanded to include the study of liver disease in people with cystic fibrosis. Up to 30 percent of patients with cystic fibrosis will develop liver disease, which can lead to cirrhosis and end-stage liver disease. To better understand the development of liver disease in patients with cystic fibrosis, CLiC has initiated studies to evaluate the natural history of cystic fibrosis liver disease (CFLD) and to identify predictors of developing liver disease in patients with cystic fibrosis and predictors of outcome in children with CFLD. In June 2009, NIDDK, in collaboration with NIH Office of Rare Diseases and the Cystic Fibrosis Foundation, convened the “Cystic Fibrosis Liver Disease Clinical Research Workshop” to discuss the prevalence, cause, diagnosis, and treatment of CFLD. An assessment of the state-of-the-science in CFLD research highlighted

the need for continued development of non-invasive methods for diagnosing and monitoring the progression of liver disease in patients with cystic fibrosis.

NIDDK-supported research conducted by ChiLDREN will lead to a better understanding of the causes and

progression of cholestatic liver diseases in children.

Advances from ongoing basic, clinical, and translational research will lay the foundation for the discovery of new diagnostic markers and innovative therapies to help improve the care of children with these diseases.

Bacteria in the Intestines Are Linked to Nutrient Metabolism and Obesity

The epidemic level of obesity in the U.S. presents an enormous impact on public health, as obesity is strongly associated with many serious diseases, such as type 2 diabetes, heart disease, and certain types of cancer. Thus, the NIH has continued to pursue a multi-dimensional research agenda on the molecular, physiological, behavioral, and environmental factors that contribute to obesity, along with research on prevention strategies and treatment of obesity. Among the many advances emerging from recent obesity research, one surprising and intriguing finding—pioneered by NIDDK-supported scientists—is that the bacteria that naturally reside in the digestive system may influence weight gain.

The human intestine is host to an enormous ecosystem of microorganisms. In fact, with a population of nearly 100 trillion, bacterial cells in the intestines outnumber human cells by almost ten to one. In exchange for a nutrient-rich environment, this bacterial community provides essential metabolic functions that humans have not developed on their own. The intimate, symbiotic relationship between the bacterial community and human physiology has even led some researchers to consider humans not as a single organism, but instead as a “supraorganism” composed of both human genes and bacterial genes. Understanding the composition of the bacterial genes and how they interact with human genes to contribute to normal health and disease has become a focal point of several NIH research initiatives.

While the presence of bacteria in the intestines and their impact on human health has been appreciated for over a century, it was only recently that researchers made a connection between the microorganisms and obesity. In 2002, Dr. Jeffrey Gordon, then a member of

NIDDK’s National Advisory Council, presented to the Council his vision of the future of digestive diseases research as encompassing the microbial world within us, and proposed that gut microbes might be associated with obesity. In 2004, Dr. Gordon and his research team at Washington University School of Medicine, in St. Louis, first published a study showing that the community of bacteria in the large intestine is an important “environmental factor” that affects how energy is extracted from the diet and stored as fat. By “transplanting” intestinal bacteria from normal mice into germ-free mice that had never been exposed to bacteria, Dr. Gordon’s team showed that the bacterial community can turn on and off host genes that are important for the production and storage of fat. This led the researchers to propose that individuals who are obese may have intestinal bacteria that are more efficient at extracting and storing energy—calories—from the diet compared to the bacterial population in individuals who are not obese.

Dr. Gordon and his colleagues tested this hypothesis in two landmark follow-up studies. In the first study, they analyzed bacterial DNA sequences to compare the types of bacteria found in the large intestine of normal mice and mice that were genetically engineered to be obese. While the intestines of both lean and obese mice were dominated by the same two major types of bacteria (*Bacteroides* and *Firmicutes*), the relative proportion of these types was different between the lean and obese mice. Subsequently, the researchers went on to show that the bacterial population in obese mice does indeed have an increased ability to extract energy from the diet. By analyzing the collective bacterial genomes, or microbiome, of lean and obese mice, they found that the microbiome of obese mice was enriched in

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energy-extracting metabolic enzymes. Additionally, when they transplanted bacterial communities from the intestines of obese mice into germ-free mice, the recipient mice (no longer germ-free) had a greater increase in total body fat compared to mice receiving transplants of bacteria from the intestines of lean mice. These ground breaking results supported a link between the composition of intestinal bacteria and obesity.

Having discovered important connections between intestinal bacteria and obesity in mice, Dr. Gordon's team has gone on to show a similar correlation in humans. In an initial study of people who are obese, the scientists found that the human intestine is dominated by *Bacteroides* and *Firmicutes* (the same types of bacteria found in mice). More importantly, the relative proportions of these types of bacteria could be modulated by weight loss through fat- or carbohydrate-restricted diets. Although the intestinal bacteria fall into these two broadly defined types, the breadth of species variation within each type is much wider among individual people. To further explore this diversity, Gordon and coworkers have most recently performed a sequencing tour-de-force of intestinal microbiomes from lean and obese twins. Despite the variation in the bacteria found in different individuals, they found a common, or "core," set of bacterial genes that are involved in various metabolic functions. Interestingly, when comparing microbiomes, the

researchers found that obesity was associated with a variation in bacterial genes involved in nutrient metabolism that may alter the energy balance in obesity.

Dr. Gordon's research provides a compelling link between the composition of bacterial genes in the intestine and excess body weight. In fact, if what was observed in mice turns out to reflect what happens in humans, Dr. Gordon's experiments with germ-free mice support a causal role for the intestinal microbial community in obesity. Additional factors might also affect the bacterial composition or their ability to extract energy from the diet to predispose an individual to obesity. In an effort to identify other potential contributing or mitigating factors, researchers are now exploring the relationships between host genetics, bacterial composition, and weight gain and obesity. While researchers pursue further advances, the current state-of-the-science offers exciting ideas about how probiotic therapies may eventually be developed to target and manipulate the resident bacteria of the intestines for the treatment and prevention of obesity. Together, research that leads to a better understanding of how nutrient metabolism is affected by intestinal bacteria and to therapeutic applications designed to target them may ultimately help reduce the public health burden associated with obesity and other conditions.

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Cynthia Griggs

A Case of Acetaminophen Overdose Triggering Acute Liver Failure



Cynthia Griggs

In February 2005, Cynthia Griggs was rushed to the hospital. A few days earlier she had come down with a nasty flu virus that had her vomiting and sweating profusely. She also had a high fever. To ease the severe aches and pains that accompanied her flu, Cynthia began taking a drug that many take in her situation, a remedy containing the pain-relief ingredient acetaminophen. Acetaminophen is the generic name of a drug found in many commonly used products available over-the-counter such as Tylenol® and Tylenol® PM, nonprescription cough and cold products such as Nyquil® and Theraflu®, as well as prescription products such as Vicodin and Percocet.

As the flu progressed, Cynthia, now age 46, recalls how she was so sick and in pain that she started popping acetaminophen tablets whenever she felt she needed them—without regard to the daily recommended dosage printed on the bottle. “I was

in such pain and perspiring so much I could hear the beads of my sweat dropping on the floor.” Her bed sheets were so soaked with perspiration that she was forced to continually switch beds.

It wasn’t long after Cynthia started taking the acetaminophen tablets that her skin started to turn yellow, a sign of jaundice indicating damaged liver function. “My mother wanted to take me to the doctor, but I told her I was fine. It was just the flu,” explains Cynthia. The next day, still very sick and in pain, Cynthia took even more acetaminophen in the form of a cold medicine. That’s when she started to become dizzy and delusional. This time her mother immediately called for an ambulance.

Though neither she nor her mother knew it at the time, Cynthia was experiencing acetaminophen toxicity, which was causing her liver to shut down in a manner that was life-threatening.

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A Frightening Episode

Cynthia arrived at the hospital in liver and kidney failure which contributed to her acting incoherently. “The doctors told my mother there was nothing they could do. My liver was in such bad shape that I only had a 30 percent chance of surviving the night.”

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But at some point in a conversation with the medical staff, Cynthia's mother happened to mention how much acetaminophen-containing medication Cynthia had taken in a relatively short period of time. Recognizing the danger that an excessive dose of acetaminophen can cause, the staff immediately injected Cynthia with N-acetylcysteine, or NAC, which, if administered within 12 hours of an acetaminophen overdose, serves as an antidote to the drug's toxicity. By the next morning, Cynthia was feeling much better. Both her liver and kidneys were beginning to function normally, and 2 days later she was discharged from the hospital.

"It was an overnight episode. The antidote saved my life," Cynthia says. But not everyone is as fortunate as she.

"The antidote saved my life," Cynthia says. But not everyone is as fortunate as she.

Taking more acetaminophen than the recommended dosage on its own can be extremely toxic to the liver, but other factors can exacerbate this toxicity. Cynthia's experience with acetaminophen had a potential additional complication, in that she had an enlarged liver, likely due to a period of increased alcohol use several years earlier. Her liver condition may have contributed to the damaging effects of the excessive amount of acetaminophen taken for her flu, which resulted in her hospitalization with what turned out to be acute liver failure.

Acetaminophen-Related Acute Liver Failure Increasing in the U.S.

The drug acetaminophen, contained in many commonly used medications, happens to be the leading cause of liver failure in the U.S. Although relatively rare, acute liver failure due to drugs, especially from acetaminophen, has occurred with

increasing frequency in the U.S. in recent years, based on findings by researchers in the NIDDK's Acute Liver Failure Study Group. Although most cases of liver injury from medications are mild and resolve quickly, some individuals develop liver injury so severe that it can lead to acute liver failure and, ultimately, death.

Other than the antidote given to Cynthia, the only treatment currently available for acute liver failure is liver transplantation, for which donor organs are in short supply. According to the U.S. Organ Procurement and Transplantation Network, currently, the number of individuals on the waiting list for a liver transplantation in the U.S. is approximately 16,000, while only about 6,300 liver transplants were performed in the U.S. in 2008, the most recent year for which complete data are available.

The majority of acetaminophen-related deaths are due to taking excessive amounts of prescription medications. U.S. Food and Drug Administration (FDA) data indicate that overdoses of nonprescription cough and cold products that contain acetaminophen occur less frequently. However, a common scenario in which overdoses do occur is when people combine these medications with other acetaminophen-containing products and unknowingly increase their ingested dose of the drug.

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Making Acetaminophen-Containing Medications Safer

Many people take acetaminophen-containing products daily to relieve pain from chronic conditions such as arthritis, or they regularly take

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products containing acetaminophen that help them sleep. When taken as directed, these products are considered to be safe. However, their safety depends on heeding the maximum daily dosage of acetaminophen—something that can be difficult to calculate when people take a combination of medications that contain acetaminophen or when they are also dealing with another liver condition. Most people do not realize that the ingredient acetaminophen is present in so many different, commonly used over-the-counter remedies, and they may thus inadvertently expose themselves to excessive amounts of acetaminophen and subsequently suffer liver failure. In fact, if a person is taking multiple acetaminophen-containing drugs, then even less than the maximum dose of each could, over the course of a day, still add up to an overdose of acetaminophen. This underscores the importance of checking medicine labels—formulations for both adults and children—for dosing, warnings, and other information, including the ingredients that are in each medicine.

In June 2009, an FDA advisory committee, made up of scientists, doctors, and consumer representatives, recommended lowering the maximum dosage of over-the-counter drugs containing acetaminophen and making high-dose acetaminophen available by prescription only. The FDA also recommended eliminating prescription acetaminophen-combination painkillers, and adding a “black-box” warning to acetaminophen-containing prescription drugs. These recommendations are intended to alert consumers to the potential for liver damage due to unintentional overdose from the drug.

Individuals who take acetaminophen-containing medications as directed, are not taking any other prescription pain medications, and do not have existing liver disease should not be at risk of damaging their livers. Alternative pain relievers such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are effective, but they too can cause

serious side-effects: when taken at high doses and for prolonged periods—especially for the treatment of chronic pain in older adults—they carry a risk of stomach ulcers and gastrointestinal bleeding. Those concerned about acetaminophen or other pain remedies should ask their doctor about which over-the-counter medicine is best for them.

Researching New Ways To Reduce Drug-Induced Acute Liver Failure

Research supported by the NIDDK has played an integral role in advancing knowledge about liver injury and acute liver failure caused by drugs such as acetaminophen. For example, the NIDDK-sponsored Adult Acute Liver Failure Study Group, founded in 1997, was based on investigator-initiated efforts to address this problem by expanding knowledge about natural history, causes, and outcomes of acute liver failure in the U.S. The Group has collected samples and data needed to conduct retrospective as well as forward-looking studies that more closely examine the problem of acute liver failure in the U.S., focusing largely on cases caused by drugs. The Group conducts clinical research at 24 sites throughout the country and is headed by Dr. William Lee at the University of Texas Southwestern Medical Center at Dallas, where Cynthia received treatment for her acetaminophen-related acute liver failure.

In 2002, the Adult Acute Liver Failure Study Group published the ground-breaking and alarming finding that liver injury due to acetaminophen use had risen dramatically in recent years to become the most frequent known cause of acute liver failure in the U.S. Building on this important observation, the Group developed an assay to directly identify cases of acetaminophen-induced acute liver failure by measuring unique compounds in the blood—an advance that could facilitate diagnosis and allow more accurate estimates of prevalence. In 2005, the Group expanded its focus to study the problem in children. The Pediatric Acute Liver Failure Study Group and the Adult Study Group are currently focusing on testing

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whether use of the antidote NAC, which can improve outcomes in cases of acetaminophen toxicity, could be expanded to cases of acute liver failure due to other causes besides acetaminophen. Recently, the Adult Acute Liver Failure Study Group published encouraging findings in the journal *Gastroenterology* showing that NAC treatment also improves survival of patients with acute liver failure due to other causes, especially in patients in the earliest stages of acute liver failure.

Another NIDDK research effort in this area, the Drug-Induced Liver Injury Network, was established in 2003 to collect and analyze cases of severe liver injury caused by prescription drugs, over-the-counter drugs, and alternative medicines, such as herbal products and supplements. This Network of five clinical centers and one data coordinating center aims to develop better tools for directly diagnosing, and ultimately preventing, drug-induced liver injury, as well as enhancing knowledge of disease processes. The Network is currently conducting a retrospective study to establish a nationwide registry of people who

experienced liver injury within the past 10 years after using one of seven specific drugs or a drug from a specific category of antibiotics. A prospective study is underway to form a nationwide registry of people who experienced liver injury after using certain drugs or alternative medicines. Also, in conjunction with the National Library of Medicine, the NIDDK is developing a Web site to release in 2010 that will feature sample cases of drug-induced liver injury based on Network data, as well as a database summarizing reports of liver injury for a given drug. This Web site will serve as a resource to aid health care providers in diagnosing, and investigators in studying, liver injury due to drugs.

Patients such as Cynthia can benefit from these and other NIDDK-supported research studies directed toward goals addressing drug- and toxicant-induced liver disease in the trans-NIH *Action Plan for Liver Disease Research* (<http://liverplan.niddk.nih.gov>). These research efforts are helping to alleviate the problem of acute liver failure caused by drugs such as acetaminophen and contribute to potentially life-saving care.

